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**WO 01/35963 A1**

(54) Title: USE OF H<sub>1</sub> ANTAGONIST AND A SAFE STEROID TO TREAT EYE CONDITIONS

(57) Abstract: Compositions and methods for treating VKC, GPC, and AKC with H<sub>1</sub> antagonists and ocularly safe steroids are disclosed.

## USE OF AN H<sub>1</sub> ANTAGONIST AND A SAFE STEROID TO TREAT EYE CONDITIONS

5       The present invention is directed to the use of an H<sub>1</sub> antagonist in combination with an ocularly safe steroid to treat ocular conditions, specifically vernal keratoconjunctivitis (VKC), giant papillary conjunctivitis (GPC), and atopic keratoconjunctivitis (AKC).

### 10       Background of the Invention

      Vernal keratoconjunctivitis (VKC), giant papillary conjunctivitis (GPC), and atopic keratoconjunctivitis (AKC) have historically been treated with a regimen of oral or topical antihistamines and/or oral or topical steroids with varying degrees of  
15       success (when used individually). Systemic treatment typically requires higher concentrations of the drug compound to be administered to afford an effective concentration to reach the necessary treatment site. Antihistamine compounds are known to have central nervous system (CNS) activity, which manifests itself in drowsiness and may have anticholinergic activity which manifests itself in the drying  
20       of mucus membranes. Steroid therapy also has significant systemic side effects, including the elevation of intraocular pressure (IOP). Topical ocular use of steroids can also cause a rise in IOP and induce cataract formation.

      Topical ocular combination therapy is known. For example, U.S. Patent No.  
25       5,192,780 (York, et al) discloses the use of an antihistamine and an antiallergic for treating ophthalmic allergic responses. U.S. Patent No. 5,149,694 (Cagle, et al.) discloses compositions of tobramycin and dexamethasone for the control of infection and inflammatory response.

30       The use of an H<sub>1</sub> antagonist in combination with a safe steroid for treating VKC, GPC, and AKC is not known.

### Summary of the Invention

The present invention is directed to compositions of combinations of H<sub>1</sub> antagonists and safe steroids to treat VKC, GPC, and AKC. Methods for the use of the compositions in mammals are also contemplated.

### Description of Preferred Embodiments

The current invention comprises compositions of H<sub>1</sub> antagonists for treating the itching, redness, and edema associated with VKC, GPC, and AKC. The compositions also include a safe steroid, as used herein the term "safe steroid" means a steroid which treats eosinophil and neutrophil associated inflammation, reduces papillae formation, and which is effective in treating inflammation without causing a clinically significant elevation in IOP.

The H<sub>1</sub> antagonists which are useful according to the present invention include all efficacious compounds, including, but not limited to: emedastine, levocabastine, mequitazine, chlorpheniramine, brompheniramine, astemizole, cetirizine, terfenadine, rocastine, loratadine, 5-[2-[4-bis(4-fluorophenyl)hydroxymethyl-1-piperidinyl]ethyl]-3-methyl-2-oxazolidinone ethanedioate) pyrilamine, clemastine, azelastine, ketotifen, olopatadine, and mapinastine.

Safe steroids which can be used herein include any glucocorticoid which meets the safe steroid definition, including but not limited to, fluoromethalone, rimexolone, loteprednol, dexamethasone betamethasone and its analogues described in U.S. Patent Nos. 5,223,493 and 5,420,120.

The H<sub>1</sub> antagonists and safe steroids (compounds) can be incorporated into various types of ophthalmic formulations for delivery to the eye. These compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution

formulations may be prepared by dissolving the compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the compound. The ophthalmic solution may also contain a thickener such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the active ingredient in a hydrophilic base prepared from the combination of, for example, carbopol-940, or the like, according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated.

The compounds are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 6.0 to 8.0. The  $H_1$  antagonists will normally be contained in these formulations in an amount 0.01% to 0.3% by weight, but preferably in an amount of 0.05% to 0.1% by weight. The safe steroids will normally be contained in those formulations in an amount 0.05% to 1.5% by weight, but preferably in an amount of 0.1% to 1.0% by weight. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye up to 4 times per day according to the routine discretion of a skilled clinician.

The preferred compositions of the present invention includes 0.01% to 0.05% emedastine and 0.1% to 1.0% dexamethasone beloxil or loteprednol.

The following example is illustrative of the composition of the present invention, but in no way limiting.

**EXAMPLE**

| <b>Ingredient</b>                    | <b>Weight %</b>       |
|--------------------------------------|-----------------------|
| Emedastine                           | 0.05%                 |
| Dexamethasone beloxil                | 0.1%                  |
| Hydroxypropyl methylcellulose        | 0.5%                  |
| Dibasic sodium phosphate             | 0.2%                  |
| Disodium EDTA                        | 0.01%                 |
| Sodium Chloride                      | 0.75%                 |
| Polysorbate 80                       | 0.01%                 |
| Benzalkonium chloride                | 0.01%                 |
| Sodium hydroxide, hydrochlorine acid | adjust to approx. 7.0 |
| Water                                | q.s. 100%             |

**We Claim:**

1. A method of treating ocular conditions in mammals selected from the group consisting of VKC, GPC, and AKC which comprises administering a pharmaceutically effective amount of a composition comprising an H<sub>1</sub> antagonist and a safe steroid.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/29436

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/55

US CL : 514/218

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/218

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| Y         | US 5,668,133 A (YANNI et al.) 16 September 1997, see the entire document.          | 1                     |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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| * Special categories of cited documents:  | *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  |
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